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November 26, 2002

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Comments on FDA's Draft Guidance [Docket No. 98D-1146]: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria on Human Health Concern

To Whom It May Concern:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on the above-captioned Food and Drug Administration (FDA) draft guidance on new antimicrobial animal drugs.

IDSA represents nearly 7,000 physicians and scientists devoted to patient care, education, research, and community health planning in infectious diseases (ID). The discipline of infectious diseases is a subspecialty of both internal medicine and pediatrics, typically involving a two-to-three year fellowship and then board certification. Infectious diseases physicians care for patients with serious infections, including persons with HIV/AIDS, meningitis, heart valve infections, severe bone, joint or wound infections, and those with cancer or transplants who have life-threatening infections caused by unusual organisms. Many of our members also are researchers who study drug resistance and are involved in the development of new and improved antimicrobial agents. As such, our goal is to ensure that patients have access to affordable and effective therapies to treat infections.

IDSA supports the recommended approach that the FDA has proposed to evaluate the safety of new antimicrobial animal agents and their microbiological effects on human health. We believe that the draft guidance represents a comprehensive approach; one that will help to provide needed certainty and clarity for sponsors of new antimicrobial agents for animals while ensuring that these products are adequately assessed for their impact on human health. The Society supports many of the items outlined in the draft guidance, particularly the qualitative risk methodology, which we consider to be an appropriate method of assessing the overall risk of a particular agent and its resistance implications on human health. Although we support this element of the proposed guidance, we would like to highlight specific concerns and recommendations.

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Currently Approved Animal Drug Products

The guidance recommends that sponsors of new antimicrobial animal drugs use a qualitative risk assessment or other equivalent studies to determine the drug's impact on human health due to antimicrobial resistance. We support the proposed assessment process outlined in the guidance for unapproved animal drugs. However, the guidance fails to adequately address the safety of antimicrobial drugs that are currently approved for use in food animals. We believe that sponsors of approved antimicrobial animal drugs should be required to evaluate the potential impact of approved products on human health in the same manner that is proposed for unapproved antimicrobial animal drugs. Thus, we recommend that the FDA require sponsors of existing drugs to develop a plan to review the safety of these products, including a timeline to ensure that such reviews are conducted in a reasonable amount of time. As this guidance is non-binding, we call on FDA to promulgate regulations to require sponsors of existing approved drugs to conduct such evaluations within a reasonable, clearly defined timeframe, and that such plans be vetted through an appropriate advisory committee or other advisory body that FDA deems suitable to evaluate such plans.

Scope of Guidance

1. FDA proposes (pg. 5, item 3) to identify the microbiological effects of an antimicrobial drug combination through the evaluation of safety data in the New Animal Drug Application (NADA) for the individual antimicrobial drugs that comprise the combination. We believe that this assumption disregards the synergistic effect that combinations may have in suppressing flora and in inducing resistance. Thus, we would urge the FDA to consider this activity when evaluating the safety of antimicrobial agent drug combinations.

Risk Assessment

2. FDA proposes (pg. 13, d.) that sponsors consider certain activities in conducting the release assessment component of the qualitative risk assessment. We believe that the assessment of an antimicrobial agent should specifically address its anaerobic spectrum. Antimicrobial agents that suppress anaerobic flora are more likely to enhance colonization by resistant bacteria by compromising the colonization resistance provided by the anaerobic flora. Thus, we recommend that the FDA include this activity in the release component of the risk assessment.

In addition, the guidance fails to require post-marketing surveillance of newly approved antimicrobial animal drugs to determine if any unexpected trends in development of resistant organisms occur in animals that receive these antimicrobials or in the humans who ingest them. We encourage FDA to include this activity, which we believe will help to validate the risk-assessment process.

3. Under the guidance, potentially all antimicrobial agents could be approved for use in food animals, even those that are of importance to human health. Human exposure through the ingestion of resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to resistant bacteria. Considering this concern, we recommend that FDA's Anti-Infective Drugs Advisory Committee and the Veterinary Medical Advisory Committee evaluate all antimicrobial agents of high importance to human health prior to approval. We believe that this approach will ensure that appropriate expertise is available to make recommendations about the human health implications of the use of these products in animals.
4. We support the ranking of antimicrobial agent classes based on their importance to human health as outlined in Appendix A - Chart A1. We agree with the ratings assigned to the various antimicrobial therapies that reflect the level of importance in human medicine with the exception of Polymyxin B. Polymyxins, specifically, colistimethate (Coly-Mycin M), have become human therapeutic agents of last resort for highly resistant gram-negative bacilli such as *Pseudomonas aeruginosa* in the past years. This agent, which was considered obsolete in the past for human use, has taken on new importance as more highly resistant gram-negative organisms emerge. As such, we recommend that a high level of importance be assigned to this drug class.

IDSA agrees that the ranking of antimicrobial agents be reassessed periodically to confirm consistency with current circumstances. However, the guidance lacks specificity as to who should be consulted to conduct the review or how often such an evaluation should be conducted. We recommend that the table be updated on an annual basis and reviewed by an advisory committee with the appropriate expertise (e.g., National Academy of Sciences).

5. The guidance does not adequately address what level of increase in human pathogen resistance levels must be seen before action is taken to limit the use of the drug in food animals or how FDA will prioritize the order by which pathogens/antimicrobial agents/food production will be reviewed. We recommend that the FDA provide specific guidance in this area.
6. While we support FDA's efforts to develop safeguards that address antimicrobial agents used in food-producing animals in the United States, we are concerned that antimicrobial use in food producing animals derived from international sources may contribute to antimicrobial resistance in the United States. The United States has steadily increased importation of food products from other countries where antimicrobial agents are used in food animal production. Although this issue is outside the scope of the guidance, it must be part of a comprehensive framework to combat antimicrobial resistance in the United States. Thus, we urge the FDA to further explore this issue and to identify and implement safeguards.

Again, we appreciate the opportunity to comment on this important draft guidance. We hope that FDA will make changes in response to the issues we have raised.

If you have any questions, or if we can provide you with additional information, please contact Robert J. Guidos, JD, IDSA's director of public policy at 703-299-0202.

Sincerely,

A handwritten signature in black ink, appearing to read "W. Michael Scheld".

W. Michael Scheld, MD
President